Traditional and pharmacologic resuscitation in traumatic brain injury: targeting inflammatory and hemostatic pathways

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Summary

In the present dissertation we aimed to investigate novel treatment modalities that may improve outcome following traumatic brain injury (TBI). We first described two clinical studies on TBI-related coagulopathy. We then investigated traditional resuscitation strategies in animal models of TBI combined with hemorrhagic shock. Finally, we investigated the use of valproic acid as new pharmacologic agent in the treatment of TBI and hemorrhagic shock. In **chapter 1** we provide an introduction to the aim of this thesis, describe the study objectives, and give an overview of the porcine model that was used for the experimental studies described in this thesis.

Part I: traumatic brain injury-related coagulopathy
In **chapter 2** we investigated the relationship between hemostatic derangements and tissue oxygenation in TBI patients. We showed that TBI-related coagulopathy is more profound in patients with metabolic acidosis and increased lactate levels. While there was no direct relationship between tissue oxygenation and coagulopathy, we observed an inverse relationship between tissue oxygenation levels and fibrinolysis. In **chapter 3** we explored which thromboelastometric hemostatic parameters could be valuable for rapid diagnosis of the severity of hyperfibrinolysis. In an *in vitro* experiment we showed that the continuous parameter lysis onset time may be used for rapid detection of severe hyperfibrinolysis, with a better resolution than the more commonly used maximum lysis index. We then confirmed these findings in a patient population with hyperfibrinolysis.

Part II: conventional treatments for traumatic brain injury and hemorrhagic shock
In **chapter 4** we investigated the effects of normal saline, colloids (Hextend [HEX]), and fresh frozen plasma (FFP) resuscitation on coagulation and endothelial systems in a clinically realistic large animal model of TBI and hemorrhagic shock. We found that normal saline resuscitation was associated with an early activation of coagulation, natural anticoagulation, and endothelial systems, compared with Hextend and fresh frozen plasma. However, it remains unknown whether fresh frozen plasma resuscitation would be beneficial in more complex clinical situations, such as polytrauma, and this constitutes the focus of the study in **chapter 5**. We showed that early administration of fresh frozen plasma decreases brain lesion size and swelling, compared to normal saline, in combined TBI and multi-system trauma. **Chapter 6** investigated the beneficial effects of

fresh frozen plasma treatment in a long-term survival model of combined TBI and hemorrhagic shock. Our data showed that early treatment with fresh frozen plasma substantially attenuates the degree of neurologic impairment, improves the rate of recovery, and preserves cognitive function in this survival model.

Part III: novel resuscitation techniques – epigenetic modulation using valproic acid

We have previously shown that addition of valproic acid (VPA; a histone deacetylase inhibitor) to the resuscitation protocol significantly decreases brain lesion size in a swine model of TBI and hemorrhagic shock. However, the precise mechanisms of this therapeutic benefit have not been well defined. As valproic acid is a transcriptional modulator, the aim of **chapter 7 and 8** was to investigate its effect on brain gene expression profiles. This high-throughput analysis of cerebral gene expression showed that valproic acid significantly modulates the expression of pathways related to cell survival and inflammation, which may explain its neuroprotective effects. The effects of valproic acid on coagulopathy are relatively unknown. In **chapter 9** we investigated the effects of valproic acid on *in vivo* platelet activation. We found that the addition of valproic acid to fresh frozen plasma resuscitation results in an early up regulation of platelet activation in the blood circulation and the brain. The previously observed neuroprotective effects of valproic acid may be due to a conservation of platelet function.

In **chapter 10**, the main conclusions of this thesis are described and discussed.